ROLE OF POSTMASTECTOMY HYPOFRACTIONATED RADIOTHERAPY AS AN ADJUVANT TREATMENT IN BREAST CANCER

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ABSTRACT

Aim : To evaluate treatment morbidities and locoregional control in breast cancer patients who were treated with adjuvant postmastectomy hypofractionated radiation therapy.

Methods : Forty female patients with breast cancer had performed modified radical mastectomy then received chemotherapy thereafter all patients were planned to receive radiotherapy with three field technique on Co 60 i.e two tangential portals for chest wall and one anterior ipsilateral supraclavicular portal for supraclavicular fossa. The total radiation dose was 39 Gy which was given as 3 Gy / fraction daily , 5 days / week. Patients were evaluated weekly during treatment and monthly thereafter. Skin, cardiac, pulmonary toxicities and lymphoedema were observed.

Results : Locoregional relapse was observed in 12.5% of patients, skin toxicities mainly of G1, 2 in 57.5 % of cases while G3, 4 was observed in 27.5 %. Radiation pneumonitis was found in 7.5% of cases. Only one case showed significant decrease in LVEF. lymphoedema mainly of G0

Conclusion : Post mastectomy hypofractionated radiotherapy showed low rate of local relapse with acceptable treatment toxicities despite higher dose per fraction. Short course of treatment decrease treatment time allowing larger number of patients to be treated per year. Further studies with larger number of patients and longer follow up periods are needed to confirm the feasibility of such treatment schedule….

Key word: Hypofractionated, Radiotherapy, postmastectomy

INTRODUCTION

Breast cancer is a major public health problem throughout the world (1).It represents 26% of all malignancies in females and is the second most common cause of cancer deaths in females(2). Modified radical mastectomy(total resection of the breast with an axillary dissection with preservation of both pectoral muscles)is the most common operative treatment for patients with invasive breast cancer (3).

Adjuvant systemic treatment in addition to local treatment has demonstrated significant improvement in survival for treated patients (4). Post mastectomy radiation therapy reduced isolated locoregional recurrence rate and improved breast cancer specific survival (5). The conventional radiation dose is 50 Gy in 25 fractions over 5 weeks with 2 Gy per fraction (4). Current radiotherapy trials of altered fractionation schedules for breast cancer seek to shorten the course of whole breast or post mastectomy radiotherapy by using hypo fractionated regimens (6). These regimens are hypothesized to be safe and effective based on pilot studies and cell culture research, suggesting that breast adenocarcinomas have a low α/β ratio (3 – 4.6 Gy) similar to that of late responding tissues , suggesting that they are more sensitive to increase dose per fraction (7), (8).

Hypofractionated radiotherapy resulted in mild early reactions and acceptable late toxicities, in addition to provide excellent long term local control (9).

One problem with standard radiation to the breast may be the extended 6 to 7-week treatment length ,so radiotherapy units often face logistical problems, such as waiting lists. Often radiotherapy departments are not available in all towns and this means that patients need to travel long distances, which is

tiring for most people ,hypofractionated regimens can be useful in solving such problems .With this treatment approach, the patients quality of life could be improved and the cost to the health system could be reduced (10,11,12).

The aim of this study was to evaluate acute and late treatment toxicities ,incidence of loco-regional recurrence in breast cancer patients who were treated with post-mastectomy adjuvant hypo-fractionated radiotherapy .

MATERIAL & METHODS

Between October 2006 to December 2007, 40 patients with breast cancer were subjected to modified radical mastectomy then were referred to Clinical Oncology Department, Zagazig University Hospitals; all patients were subjected to thorough clinical examination laboratory and radiological investigations. The patients should be free as regard local or distant metastasis. Adjuvant chemotherapy was completed before the beginning of radiation therapy. Table (1) shows the patients criteria.

Table (1) : patients criteria

Total number of patients		number	%
Age (year)		25 – 70	(median 50)
Menopausal status → pre		25	62.5%
→ post		15	37.5%
T stage →	T2	10	25%
	T3	17	42.5%
	T4	13	32.5%
N stage	N1	17	42.5%
	N2	23	57.5%
Histology:	IDC	37	92.5%
	special	3	7.5%
ER States:	→ positive	32	80%
	→ negative	8	20%
PR States	→ positive	30	75%
	→ negative	10	25%
Chemotherapy	FAC	28	70%
	CMF	12	30%

All patients were females with a median age of 50 years. 62.5% of patients were in the premenopausal period, while 37.5% were post-menopausal, stage IIIA was 67.5 %, stage IIIB was 32.5%. Histologicaly 92.5% of cases had invasive ductal carcinoma. ER positive in 80% of cases and PR positive in 75% of cases. Adjuvant chemotherapy was given to the patients 70% received FAC (5 Fu, adriamycin, cyclophosphamide) the other 30% received CMF (cyclophosphamide, methotrexate, 5 Fu) when there was contraindication to adriamycin. Hormone

receptor positive patients received hormonal therapy .

Patients were planned on 2D planning system and treated on Co 60 machine . Two tangential portals for chest wall were planned on simulator with lung slice not exceeding 2.5 cm. Direct anterior field to the supraclavicular fossa was planned with 0.5 cm gap junction from tangential fields. Superior divergence of tangential portals was eliminated by 5° couch rotation. Inferior border divergence of anterior nodal field was removed by moving the gantry a few degrees following a 90° couch rotation. The lung and heart slice included in the tangential portals and brachial plexus in the nodal fields received the full prescribed dose. The dose of irradiation was 39 Gy delivered in 13 fractions. Written consent was taken before starting the treatment.

Patients were evaluated at least once a week during radiotherapy(RT), and every month thereafter. Skin reactions, respiratory symptoms and evidence local relapse should be evaluated at each follow up visit. A chest x-ray was done prior to radiotherapy, twice during first year of follow up and then at 6 months interval ,chest CT was performed when abnormal shadow was detected in chest x-ray to assess pulmonary toxicity. Bone scan, abdominal ultrasound, were done routinely annually.

* Skin reactions were categorized according RTOG recommen dation.(13)

RTOG: 1 Faint or dull erythema with epilation, decreased sweating, drying, reddening, tingling, itching and warmth.

RTOG: 2 Tender or bright erythema with patchy moist desquamation with moderate oedema.

RTOG : 3 Confluent moist desquamation, the inflamed epidermis may slough leaving painful denuded areas of dermis exuding serum.

Echocardiography of all patients was done before RT and at 2 months after radiation. A fall of more than 10% in ejection fraction(EF) was taken as a significant reduction, patients who had a base line EF less than 60% were not included in the trial. Lymphoedema was taken as a clinical finding any injury to brachial plexus was documented.

Statistical analysis :

RESULTS

The range of follow up was 12 – 48 months with a median of 36 months. Loco-regional relapses developed in 5 cases (12.5%). Of the relapsed cases , mastectomy scar was the most common site of relapse (60%) while (40%) relapsed in axilla. Distant metastasis were seen in 8 cases (20%) .Mortality due to the disease occured in 3 cases (7.5%). The overall survival at the end of follow up period was 90%. While disease free survival was 67.5% (fig 1,2)

As regard skin reaction, G1 was observed in 32.5% of cases, G2 in 25%, G3 in 22.5% and G4 in 5% of cases, only one case (2.5%) had developed more than 10% drop in LVEF radiation pneumonitis was observed in 3 cases (7.5%) which developed 4.5 months after the end of radiotherapy. Two cases were asymptomatic and one case developed mild cough. Sore throat and dysphagia was observed in 15% of cases which improved to some extent by symptomatic treatment. G0 lymphoedema was seen in 57.5% of cases, G1 in 25%, G2 in 12.5% and G3 in 5%. No cases showed damage or weakness of brachial plexus.

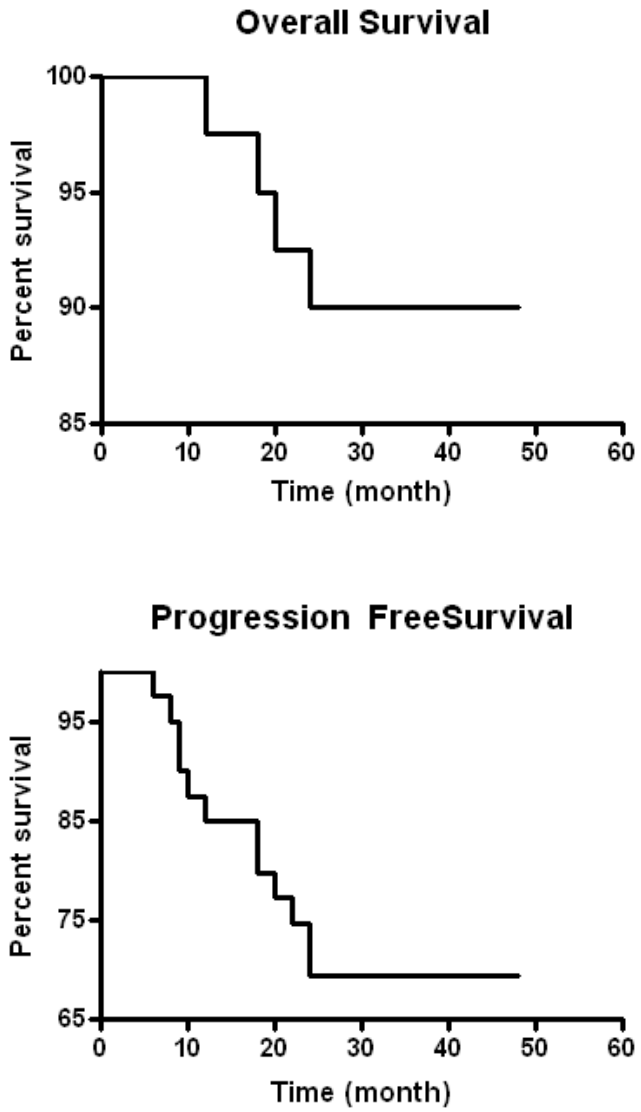

Figure (2)

DISCUSSION

Breast cancer is considered to be closer to late reacting tissues and thus larger fractions are effective in controlling locoregional disease (14) shorter radiation course based on radiobiologic models offer the promise of equivalent local control to conventional radiation therapy by giving larger doses per fraction in shorter periods of time (15). Many reports emphasized that shorter fractionated schedules were an acceptable alternative to the more traditional longer schedules (16). Hypofractionation could be proposed as a simple way to shorten treatment time(17).

A comparative study (18) was performed using three hypofractionated protocols as a post-mastectomy adjuvant radiotherapy in breast cancer (5.4 Gy in 5 fractions vs 3.5 Gy in 10 Fractions vs 2.66 Gy in 15 fraction) skin reactions were more sever with 5 fraction arm than with 15 fraction arm (26% vs 11%). It is quiet obvious that the reaction with 15 fraction were mainly > 85% G1 and G2 while G4 skin reaction was 3 folds higher in one week arm than the three weeks arm (11% vs 3%) the rate of reactions in the ten fractions arm was in between the other two arms. Our study showed similar results as

regard skin reaction most cases showed G1, G2 skin reaction in 57.5% G3 in 22.5% of cases and only 5% of cases showed G4 reaction.

Read et al (19) reported moderate skin reactions developed in 15% of patients given a total dose of 40 Gy in 15 fractions, sever desquamation was observed in 6% of cases with large areas of wet desquamation but they suggested that the incidence of skin reaction was clearly related to the use of bolus, so the study of Osamu et al (16) showed no sever skin reaction as they didn't use bolus. Clark et al (20,21) reported an equal relapse rate and highly similar cosmotic results in patients treated with 40 Gy in 16 fractions of 2.5 Gy or with 50 Gy in 25 daily fractions of 2 Gy. The hypofractionated schedule used by Livi et al (11) was effective in terms of local control, with only 1.8% of breast relapse. The START (22) group had performed a study where patients were randomized to a 50 Gy total dose of radiation in 25 fractions over 5 weeks or 41.6 Gy or 39 Gy in 13 fractions of 3.2 Gy or 3 Gy respectively. After a median follow up of 5.1 years the loco-regional relapse was 3.6% in conventional group and 3.5% with 41.6 Gy regime and 5.2% with 39 Gy in 13 fraction. Abubaker et al (18) who compared three hypofractionated protocols showed leocoregional relapse from 10 – 12% and clearly proved that shorter treatment protocols were effective in controlling local relapse rate, our study showed 12.5% locoregoinal relapse which greatly coincide with the study of Abubaker et al (18).

Factors that influence the development of pulmonary radiation reactions relate to RT technique (the volume of lung irradiated and total dose and fraction size of radiation) with the combination, timing and intensity of chemotherapy (23). Yoden et al (25) reported 15% radiation pneumonitis while Osamu(16) reported 6% radiation pneumonitis. Abubaker et al (18) reported 4.5% radiation pneumonitis. Our study showed 7.5% radiation pneumonitis, increase fraction size didn't affect the incidence of radiation pneumonitis as compared with the above mentioned studies. In our study only one case 2.5% showed more than 10% drop in LVEF while In the study of Abubaker (18) 5.6% of cases showed drop of LVEF > 10%. Combination of axillary dissection and radiotherapy showed higher incidence of arm edema (24). In our study ,only 5% showed G3 lymph-edema.

Appearance of skin telangiactasia ,fibrosis and induration worsen the final cosmotic outecome (25) we have not observed signficant skin telangiaectasia, fibrosis,or induration.

Hypofractionated schedules have the advantage of allowing a larger number of patients to be treated per year and therefore shortening waiting list with reduction in cost to the health system(11). In conclusion, postmastectomy adjuvant radiotherapy, using 39 Gy as a total dose with 3 Gy\fraction daily ,5 days\week , in breast cancer has an acceptable acute morbidity, low rate of local relapse and low rate of late toxicity despite a higher dose per fraction. This short course of treatment allow larger number of patient to be treated per year, and lessen the burden of treatment for patients, most of them suffer from long term adjuvant therapy. Our study support this opinion but we recommend further studies with larger number of patients and longer follow up periods to support the possibility of making adjuvant hypofrationted radiotherapy an alternative to conventional radiotherapy in the treatment of breast cancer.

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